Amendments to the Specification

Replace the paragraph beginning on page 3, line 5 with the following amended paragraph:

In another embodiment, the present invention comprises a method of treating a mammal in need of modulation of bone formation. ~~which~~ The method comprises administering to the mammal a suitable amount of ~~BMIP-3~~ BMP-3. Administration may be in conjunction with a suitable matrix.

Replace the paragraph beginning at page 8, line 7, with the following amended paragraph:

A BMP-3 polypeptide may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. Antigenic peptide fragments of the antigen for use as immunogens include, *e.g.*, at least 7 amino acid residues of the amino acid sequence of the amino terminal region~~, such as an amino acid sequence shown in SEQ ID NO:~~, and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

Replace the paragraphs beginning at page 35, line 31 to page 39, line 5 with the following amended paragraphs:

Methods of Identifying Promoters and Inhibitors of Bone Growth Using BMP-3

The invention further includes methods for developing BMP-3 inhibitors or antagonists which method involves screening for molecules which inhibit BMP-3 function or the transcription or translation of BMP-3. Such screening procedures are within the skill in the ~~an~~ art. Such a screening assay for detecting the BMP-3 inhibiting activity of a molecule would typically involve mixing the potential inhibitor molecule with an appropriate substrate, incubating and determining the extent of inhibition. Various substrates may be designed for use in the assay. In ~~addition.~~ addition, BMP-3 polypeptides may be used for ~~structure-based~~ structure-based design of BMP-3 inhibitors. A particular method of the invention comprises analyzing the three dimensional structure of BMP-3 for likely substrate binding sites and synthesizing molecules incorporating a reactive binding site.

The invention will be further illustrated in the following non-limiting examples.

EXAMPLE 1. Production of Retroviral BMP-3

A retroviral system was used to produce BMP-3 and to test its effects in mouse osteoprogenitor cells which respond to BMP treatment by expressing markers associated with osteogenic differentiation (Thies et al., Endocrinology 130: 1318-24, 1992; Engstrand et al., Hum. Gene Ther. 11: 205-11, 2000).

Replace the paragraph beginning on page 41, line 17, with the following amended paragraph:

BMP-2 promotes commitment of C2C12 cells to the osteoblastic lineage, (Katagiri et al, J. Cell Biol. 127, 1755-1766, 1994). To determine whether BMP-3 influences this activity of ~~BIvIP-2. the~~ BMP-2, the effects of BMP-3 on Msx2 expression were monitored. Msx2 is a direct target of BMP signaling in some cells (Holinagel et al., J. Biol. Chem. 274, 19838-45, 1999). C2C12 cells (ATCC) were maintained in DMEM plus 15% FBS. Cells were grown to confluence and switched to differentiation medium (DMEM plus 5% FBS) in the presence or absence of ~~TGFb2~~ TGFβ (1 ng/ml, R&D Systems) or rhBMP-2 (300 ng/ml). Total RNA was prepared using the Uneasy kit (Queen). 10 mg was loaded per lane. A fill-length cDNA encoding Msx2 was used as a probe. Myosin light chain 2 (Mlc2) and osteocalcin (OC; Bglapl) probes were used as markers for myogenic and osteogenic differentiation, respectively. Equal loading was verified by hybridization to a mouse glyceraldehyde-3-phosphate dehydrogenase (Gapd) probe. BMP-2 induces Msx2 expression in C2C12 cells. In contrast, no Msx2 induction was seen in untreated cells stimulated to undergo myogenic differentiation, and a low level of expression is seen in cells treated with ~~TGFb~~ TGFβ, which prevents differentiation (Katagiri. T. et al.. J. Cell Biol. 12.2. 1755-66, 1994). Therefore, induction of Msx2 is an early response to BMP-2-mediated commitment to the osteogenic pathway.

Replace the paragraph beginning on page 42, line 3, with the following amended paragraph:

To examine whether BMP-3 influences ~~.Msx2~~ Msx2 induction, 2 kb of the Msx2 promoter was used to drive a luciferase reporter (Liu et al., Proc. Nat. Acad. Sci.. (USA) 92: 6137-41, 1995). C3H l0Tl/2, MC3T3-E1, or P19 cells were seeded at 1 X 10^5 cells per 3.5 cm dish for 24 hours prior to transient cotransfection with 2kb Msx2-Lux or p3T3-Lux, pCINeo-

BMP-3, or pCINeo (control), and a β-galactosidase control using Superfect (Qiagen). For the inhibition assays, the cells were incubated for l6h in 30-fold BMP-3- or 30-fold control-CM prepared as described above, 3 h after transfection, in the presence or absence of rhBMP-2 (100 ng/ml). Luciferase activity was assayed using the Luciferase Assay System (Promega) and normalized for transfection efficiency with β-galactosidase. Experiments were performed three times in triplicate. BMP-2 induces Msx2 reporter expression in C3H l0T1/2 cells (FIG. 2D, columns 1 and 2), but BMP-3 CM abolishes this induction (FIG. 2D, column 3).

Replace the abstract on page 48, line 4, with the following amended abstract:

Methods and compositions are provided for the treatment of defects and disease involving osteoporosis, or osteopenic conditions. The methods ~~comprises~~ comprise applying to the site of osteoporotic or osteopenic conditions a composition comprising ~~aBMP-3~~ a BMP-3 inhibitor or antagonist. The invention further provides methods and compositions for modulating or regulating the formation of bone utilizing BMP-3 compositions.

Replace the paragraph beginning on page 43, lines 2, with the following amended paragraph:

To examine BMP-3 function in vivo, BMP-3 mice were generated. BMP-3 clones were isolated from a 129/Sv genomic DNA library (Stratagene). The targeting vector was constructed by replacing a 3.8 kb fragment containing exon 2 with the neomycin-resistance gene (pMC-neo; Stratagene). A thymidine kinase gene cassette (pMC-tk) was inserted upstream. The linearized targeting vector was introduced into J1 ES cells by electroporation. Targeted clones were injected into C57B1/6 blastocysts. RT-PCR was performed on RNA isolated from BMP-$3^{+/+}$ and BMP-$3^{-/-}$ newborns as described (Bostrom et al., J. Orthop. Res. 13. 357-367 (1993). BMP-3 primers

were as follows: 5'- GGACAGACGCTGCTATT-3' (SEQ ID NO:~~7~~8) and 5'-TGTTCTACGACTCACTC-3' (SEQ ID NO:~~8~~9). BMP-3-specific products were analyzed by Southern blot analysis using a ~~BNW~~BMP-3 cDNA as a probe. The colony was maintained on an outbred (CD-1) background.

Replace the pending Sequence Listing at the end of the specification with the enclosed sequence listing (pages 1-16).